" SYNTHESIS, ANTIMICROBIAL SCREENING AND MOLECULAR DOCKING STUDIES OF NOVEL DERIVATIVES OF 1,2,4-TRIAZOLE AND 1,3,4-THIADIAZOLE "

SYNOPSIS

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1. INTRODUCTION

1.1 Introductory parts of Research Topic:

A survey of literature reveals that, 'Heterocycles' make up an exceedingly important class of compounds. The nature has provided vast number of biologically important compounds like carbohydrates, proteins, amino acids, polymers, steroids, etc. Usually they contain one or more than one heterocyclic rings or chains. Ever since such naturally occurring compounds are known, man has adventured to unravel the separation, purification, identification and assign proper structure to such compounds. Further, man has been trying to copy the important structural part of such molecules in order to find out more useful drugs.

Medicinal Chemistry is a science whose root lies in all branches of chemistry and biology (Alfred Burger,1970:01). The discipline of medicinal chemistry is devoted to the discovery and development of new agent for treating diseases (Wilson, 1998:01). Though this millennium has evolved a high sophisticated level in the field of science and technology, the awareness and eradication of diseases like HIV, Tuberculosis have been a great challenge to scientist. As Schiller wrote (Alfred Burger,1970:02)," To one man science is the highest the heavenly Goddess to another it is a proficient cow that supplies him with butter."

The field of medicinal chemistry has evolved from an emphasis on the synthesis, isolation and characterization of drug to an increased awareness of the biochemistry of disease states and the design of the drug for the prevention of disease (Remington,2000:458), Investigation in medicinal chemistry are undertaken as an adventure of human spirit, stimulated largely by curiosity and served by disciplined imagination(Weaver,1967:55,3). The recent advancement like Drug designing, combinatorial chemistry, computational chemistry, molecular biology and genetic engineering make interesting the chemistry approach.(Wilson, 1998:02).

Triazole ring is a quite important five-member heterocycle with three nitrogen atoms, possesses aromaticity and rich electrons. This type of unique structure endows triazole derivatives to readily bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions such as coordination bonds, hydrogen bonds, ion-dipole, cation stacking, hydrophobic effect, van der Waals force and so on, and thus display a broad spectrum of biological activities.(Mi, 2008:84-86 and Wang, 2011:1429-1456) Furthermore, triazole ring is able to be used as an attractive linker to provide a convenient and efficient way

to combine different pharmacophore fragments to produce an innovative bifunctional drug molecules, this has been an unusually outstanding strategy to develop various bioactive and functional molecules. In addition, triazole ring is also widely used as an isostere of imidazole, oxazole, pyrazole, thiazole, amide moiety etc. to design various types of new drug molecules and improve the biological activities.

Five membered heterocyclic compounds show various types of biological activity among them 2,5-disubstituted 1,3,4-thiadiazoles are associated with diverse biological activity probably virtue of –N=C-S- grouping. Therapeutic importance of these rings prompted us to develop selective molecules in which substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities. Thiadiazoles have occupied an important place in drug industry, 1,3,4-thiadiazoles have wide applications in many fields. Earliest uses were in the pharmaceutical area as an antibacterial with known sulphonamides drugs (Vasoya, 2005:33-36).

1.2 NEED FOR THE PRESENT STUDY:

The increasing emergence of multidrug-resistant strains recently especially the explosion of New Delhi metallo-β-lactamase 1 (NDM-1) superbugs in many countries (England, USA, Japan, Sweden, Holland, Australia, China etc.) in 2010 has led to most of the first-line clinical antibiotics ineffective. Thus, the development of novel antimicrobial agents has become an urgent mission all around the world (Yuan, 2007: *16*, 343–350 and Wang, , 2010: *19*, 30–39). In recent decades, many researchers devoted to the introduction of different heterocycles such as oxazole, pyrimidine, isoxazole etc. into antibacterial molecules to get new drugs like Sulfadiazine and Linezolid. It was well known that the development of triazole antifungal drugs has achieved unprecedented success, while the researches of triazole compounds as antibacterial agents are relatively late. A large number of discoveries depicted that introduction of triazole ring into antibacterial drugs is helpful for the reduction of drug resistance and enhancement of antibacterial potency. Especially new types of antibacterial compounds, constructed by the 1,2,3-triazole ring, have been attracting special attention and gradually becoming a new highlight field for the development of antibacterial drugs.

Tuberculosis (TB) has become one of the leading public health threat worldwide. Until now, there has already been one-third of the world's population infected with Mycobacterium tuberculosis (M. tb) and the number of the infected people is still increasing (Maddry,2009: *89*, 354–363). Although some efficient anti-TB agents like isoniazide and rifampin with favorable bioactivity against M. tb were successfully exploited over the past few decades, there is still an emergency need for more effective drugs due to the global prevalence of drug-resistant TB (XDRTB) and multidrug resistant TB (MDRTB) as well as the increase of the infectious probability of people with AIDS. Recently, some heterocycles including quinolines, nitroimidazoles and pyrroles are reported to be antituberclar candidates (Sarkar, 2011:*14*, 148–161.). Specifically, many heterocyclic triazoles display outstanding anti-TB potential.

2. LITERATURE REVIEW

The through literature survey through Internet browsing, MEDLINE, CDROM search, chemical abstracts, scientific journals and textbooks emphasizes that there is extensive need to develop potential antibacterial and antitubercular drugs. The literature survey also indicates variety of synthetic routes, various procedures for biological testing and property study. Therefore there is tremendous scope to exploit thiadiazole and triazole nuclei. Here in this section, we discussed some examples, which highlight the biological importance of stated molecules.

2.1 1,2,4-TRIAZOLE:

2.1.1 Anti bacterial activity:

2.1.1.1. Shi, Y.,*et al.*, (2011), studies the researches of 1,2,4-triazoles as antifungal agents have made major breakthrough, the exploitations of them as antibacterial agents were relatively late and so far no 1,2,4-triazole antibacterial agents were successfully developed. However, some 1,2,4-triazole compounds including mono-1,2,4-triazoles, bis-1,2,4-triazoles and multi-1,2,4-triazoles have been found to have antibacterial potential in recent years, which brought new hope for 1,2,4-triazoles as antibacterial agents. A series of new coumarin-based mono-1,2,4-triazole derivatives were designed and synthesized, the antimicrobial evaluation showed that some prepared coumarin triazoles displayed comparable or even better antibacterial efficacy in comparison with reference drugs enoxacin and chloromycin.

2.1.1.2. Bhandari, K.,*et al.*,(2009), concluded Mono-triazoles 1a-d exhibited better activities than their precursor coumarin bromides, while bis-triazole 2 exhibited stronger antibacterial and antifungal efficiency than its corresponding mono-triazole. These results

manifested that heterocyclic 1,2,4-triazole moiety exerted important influence on antibacterial activities.

Oxiconazole is an antifungal drug for external use but does not show antibacterial activity. Restriction the free movement of azolylethyl chain of oxiconazole with a six member ring and replacement the imidazole ring with 1,2,4-triazole moiety, which yielded derivatives 3a-b, exhibited potent antibacterial activity and surprisingly none of them was active against fungal strains. Compounds 3a and 3b displayed equivalent bioactivity against S. aureus activity in comparison with that of current clinical drug gentamycin with MIC value of 6.25 *µg/ml.*.

2.1.1.3. Kim, O.K., *et al.,* (2011), studied Triazole derivative **4** demonstrated inhibitory activity against LcrF (a MAR transcription factor) which regulates virulence in *Yersinia pestis* and *Yersinia pseudotuberculosis* with IC50 value of 35.7 *µg/ml.* in a primary cell-free LcrF-DNA binding assay as well as in a secondary whole cell assay. The results confirm that this compound is an effective antivirulence agent and has the potential to prevent infections caused by *Yersinia spp.*

2.1.1.4. Wan, K. *at el.*, (2010) concluded A series of halobenzyloxy and alkoxy were introduced into 1,2,4-triazole ring and the antibacterial tests revealed that some synthesized triazoles carrying dihalobenzyloxy, octyloxy or dodecyloxy groups exhibited moderate antimicrobial activities *in-vitro*. Noticeably, the difluorobenzyloxy triazole **5** and it's hydrochloride showed the most potent activity against *P. aeruginosa* and *E. coli* with MIC values of 112.5 and 56.25 *µg/ml.* respectively.

2.1.1.5. Atia, A.J.K., (2009) Triazole derivative **6**, with a nitroimidazole ring combined with triazole moiety, exhibited higher inhibitory activities against *S. aureus*, *Bacillus proteus* and *E. coli* than other heterocycle substituted compounds. Quinolone-derived 1,2,4-triazole

7 displayed very good antimicrobial activity, comparable to the first line standard drugs norfloxacin.

2.1.1.6. Ezabadi, I.R.; *at el.,* (2008) Sulfanilamide 1,2,4-triazole **8** showed the same antibacterial activity as the commercial agent streptomycin against *E. coli*, *Bacillus cereus*, *Micrococcus flavus* and *Staphylococcus epidermidis*. Furthermore, these compounds showed higher bactericidal effect than chloromycin. The researchers also found that Gram-negative bacteria seem to be more sensitive to these compounds than Gram-positive species.

2.1.1.7. Hu, G.Q., *at el.,* (2006) studied Amino-containing oximer ether triazole **9** exhibited significant anti-*Escherichia coli* activity with MIC value of 1.0 *μg/ml.*, which was lower than that of reference drug norfloxacin.

2.1.2. Antitubercular Activity:

21..2.1 Marrapu, V.K., *at el.,* (2011) studied A lot of compounds with 1,2,4-triazole ring in combination with other heterocycles possess antitubercular activities.

2.1.2.2 Zampieri, D., *at el.,* (2011) studied Indolyl-derived triazole **10** exhibited good antitubercular activity, which is slightly weaker than clinical drug rifampin.

2.1.2.3. Patel, N.B. *at el.,* (2009) studied Benzothiazole-based 1,2,4-triazoles showed excellent antitubercular activity. Specially, compound **11** with good activity against H37Rv strain (MIC = 25 *μg/ml.*), was a good choice for the preparation of new derivatives in order to improve antitubercular activity in future.

2.1.2.4. Jadhav, G.R *at el.,* (2009) studied Fuorobenzimidazoles derivatives **12a** and **12b** exhibited significant antimycobacterial activity against the H37Rv strain with MIC values of 0.36 and 0.58 *μg/ml.*, respectively, which showed the promising antimycobacterial activity.

2.1.2.6. Suresh Kumar, G.V *at el.,* (2010) studied Some triazolyl-thiols and triazolyl-thiones exhibit noticeable antitubercular activity.

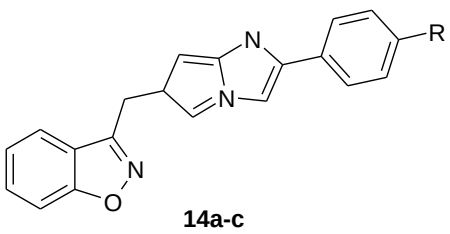
2.1.2.7. Gobis, K. *at el.,* (2010) studied Thiazolyl-derived triazole-thiol **13a** showed significant antitubercular ability with MIC value of 0.39 *μg/ml.*, which was similar to rifampicin. Isopropylthiazole clubbed triazole compound **13b** exhibited 2-fold enhanced potency than precursor carbohydrazide.

2.2. 1,3,4-THIADIAZOLE:

2.2.1. Anti bacterial activity:

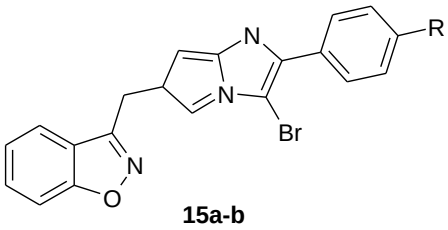
2.2.1.1. Wujec, M *at el.,* (2008) studied The usefulness of 1,3,4-thiadiazole as a privileged system in medicinal chemistry has prompted the advances on the therapeutic potential of this system. 1,3,4-thiadiazole derivatives posses interesting biological activity probably conferred to them due to strong aromaticity of the ring system which leads to great *in vivo* stability and generally, a lack of toxicity for higher vertebrates, including humans when diverse functional group that interact with biological receptor are attached to aromatic ring.

2.2.1.2. Imtiyaz Ahmed M. Khazi *et.al.,(*2009) were synthesized novel methylene bridged benzisoxazolyl imidazo [2, 1-b][1,3,4]- thiadiazoles. The investigation of antibacterial screening revealed that some of the tested compounds showed moderate to good bacterial inhibition. Particularly compounds **14a, 14b, 15a, 15b** and **16a** have shown very good antibacterial activity. Compound 69a has exhibited highest antibacterial activity. The high activity is attributed to the presence of electron withdrawing chloro- and bromofunctional groups.



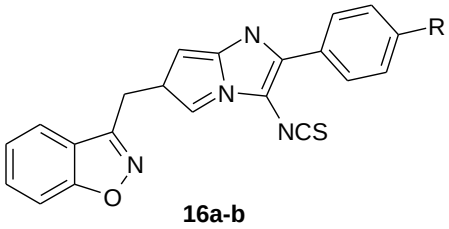
14a-c

a, R = Cl; b, R = Br; c, R = 3-Comarinyl



15a-b

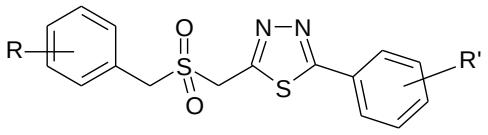
a, R = Cl; b, R = NO_2



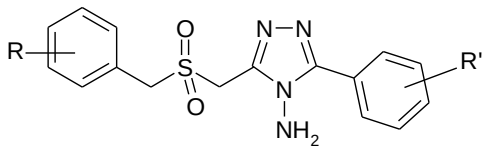
16a-b

a, R = Cl; b, R = OMe

2.2.1.3. Mihai Barboiu *et.al.*, (1996) have found that 2-(arylmethanesulfonylmethyl)-5-aryl-1, 3, 4 thiadiazoles **17a–d**, 3-(arylmethanesulfonylmethyl)-5-aryl-4H-1,2,4-triazol-4-amines **18a–d** exhibited high activity (22–39 mm) on both Gram (+ve) and Gram (-ve) bacteria. In fact, compounds **17d** and **18d** showed pronounced activity (31–39 mm) towards Gram (+ve) bacteria.



17a-d



18a-d

a; R = H,R' = H
b; R = H, R' = 2-Cl
c; R = 4-Cl, R' = H
d; R = H, R' = 2-Cl

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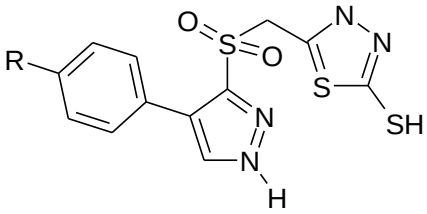
2.2.1.4. V. Padmavathi *et.al.* (2009) also reported synthesis and biological screening of some novel sulfone-linked bis heterocycles. In which the compounds 72a showed excellent activity against Gram-positive bacteria (inhibitory zone >25 mm), good activity against

Gram-negative bacteria (inhibitory zone >20 mm). The compounds **19a-c** showed high inhibitory effect towards tested fungi.



19a-c

a; R = H, b; R= Me, c; R = -Cl

2.2.2. Antitubercular Activity:

2.2.2.1. S. Karakus *et.al.,(*2002) have found that one of the thiadiazole derivative, namely 2-(4-chlorophenylamino)-5-(4-aminophenyl)-1, 3, 4-thiadiazole **20**, showed 57% inhibition against Mycobacterium tuberculosis .Further They exhibited higher inhibitory activity against T47D cells (human breast cancer cells) than cisplatin.

2.2.2.2. Johnson *et. al. (2006)* synthesized 3-(2-sulphido-1,3,4-thiadiazolium-4-carbonylphenyl) syndones and 4-(4-(2-sulphido-1,3,4-thiadiazolium)benzoyl)-1,3,4-thiadiazolium-2-thiolates from 3-(4/3-(hydrazine carbonyl)phenyl) syndones, and their antimicrobial and antitubercular activity against *M. tuberculli* using standard drug Cotrimoxazole and Fluconazole at concentration 100 *µg/ml.*.

From the above literature review it is clear that there is a ample of scope to generate novel antimicrobial and antitubercular drugs and in continuation of our research for novel bioactive molecule, we thought it is worthwhile to synthesize and carry out said biological evaluation of some novel derivatives of 1,2,4- triazole and 1,3,4- thiadiazole.

3. AIM AND OBJECTIVE

- To carry out extensive review of literature to understand;
    - Synthetic methods for triazole/thiadiazole.
    - Potential of triazole/thiadiazole as chemotherapeutic agents.

- Synthesis of the derivatives of triazole/thiadiazole;
    - Development and standardization of the methods to synthesize the newer analogs of triazole/thiadiazole
    - To establish the isolation and purification techniques for synthesized compounds.

- To characterize the synthesized compounds employing different spectral tools and elemental analysis.
- To study the current status of existing thiadiazole and triazole in anti-infective therapy.
- To study the properties of the newer compounds.
- To evaluate the synthesized compounds for appropriate pharmacological activity using suitable methods.
- To investigate the pharmacological action of synthesized compounds by Molecular Docking and QSAR study.

4. PLAN OF WORK

4.1. Literature survey

4.2. Procurement of Drugs and Excipients

4.3. Formulations Method of Research Topic

4.3.1. Synthesis

The newer compounds will be synthesized in our laboratory using appropriate synthones.

4.3.2. Purification and Physical Constants

The physical constants like solubility in various solvents, melting point, boiling point, nature of crystals, color and percentage yield will be obtained after purification by recrystallization in the suitable solvent or column chromatography using suitable medium for packing columns as described in literature.

4.3.3. Spectroscopic studies

The structure of the synthesized compounds will be established on the basis of spectroscopic data and physical data. Ultra Violet spectrum will be studied by JASCO V-530 spectrophotometer, Infra Red spectra (KBr-Nujol0 will be recorded for the identification of various functional groups. HNMR (δppm) will be recorded using TMS as an internal standard. MASS spectra of some selected compounds will be obtained to confirm the final molecular structure

4.3.4.. **DOES THE STUDY REQUIRE ANY INVESTIGATION OR INVERVENTIONS TO BE CONDUCTED ON PATIENTS OR HUMANS OR ANIMALS? ------- NO----------**

4.3.5.. **HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF ---------**

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